This report is required by law (7 USC 2143). Failure to report according to the regulations can result in an order to cease and desist and to be subject to penalties as provided for in Section 21!

See attached form for additional information.

Interagency Report Control No.:

UNITED STATES DEPARTMENT OF AGRICULTURE
ANIMAL AND PLANT HEALTH INSPECTION SERVICE

1. CERTIFICATE NUMBER: 51-F-0024
CUSTOMER NUMBER: 12776

FORM APPROVED
OMB NO. 0579-0036

ANNUAL REPORT OF RESEARCH FACILITY

(TYPE OR PRINT)

Center For Biologics Evaluation & Research
29 Lincoln Drive
Bethesda, MD 20852

NOV 28 2005

Telephone: (b)(6), (b)(7)c

3. REPORTING FACILITY (List all locations where animals were housed or used in actual research, testing, or experimentation, or held for these purposes. Attach additional sheets if necessary)

FACILITY LOCATIONS (Sites) - See Alached Listing

REPORT OF ANIMALS USED BY OR UNDER CONTROL OF RESEARCH FACILITY **(Attach additional sheets if necessarv or use APHIS Form 7023A)**

A. Animals Covered By The Animal Welfare Regulations	B. Number of animal being bred, conditioned, or held for use in teaching, testing, experiments, research, or surgery but not ye used for such purposes.	C. Number of animals upon which teaching, research, experiments, or tests were conducted involving no pain, distress, or use o pain-relieving drugs.	D. Number of animals upon which experiments, teaching, research, surgery, or tests were conducted involving accompanying pain or distress to the animals an for which appropriate anesthetic, analgesic, or tranquilizing drugs were used.	E. Number of animals upon which teaching, experiments, research, surgery or tests were conducted involving accompanying pain or distress to the animals and for wh the use of appropriate anesthetic, analgesic, or tranquiliz drugs would have adversely affected the procedures, res or interpretation of the teaching, research, experiments, surgery, or tests. (An explanation of the procedures producing pain or distress in these animals and the reasc such drugs were not used must be attached to this report	F. TOTAL NUMBER OF ANIMALS (COLUMNS C + D + E)
4. Dogs					
5. Cats					
6. Guinea Pigs	0	282	165	13	460
7. Hamsters	0	0	614	0	614
8. Rabbits	0	98	0	0	98
9. Non-human Primates	12	62	5	0	79
10. Sheep	0	8	0	0	8
11. Pigs					
12. Other Farm Animals					
13. Other Animals					
Ferrets	0	15	0	0	15

ASSURANCE STATEMENTS

1) Professionally acceptable standards governing the care, treatment, and use of animals, including appropriate use of anestetic, analgesic, and tranquilizing drugs, prior to, during, and following actual rese teaching, testing, surgery, or experimentation were followed by this research facility.

2) Each principal investigator has considered alternatives to painful procedures.

3) This facility is adhering to the standards and regulations under the Act, and it has required that exceptions to the standards and regulations be specified and explained by the principal investigator and ap Institutional Animal Care and Use Committee (IACUC). **A summary of all such exceptions is attached to this annual report.** In addition to identifying the IACUC-approved exceptions, this summary inc brief explanation of the exceptions, as well as the species and number of animals affected.

4) The attending veterinarian for this research facility has appropriate authority to ensure the provision of adequate veterinary care and to oversee the adequacy of other aspects of animal care and use.

CERTIFICATION BY HEADQUARTERS RESEARCH FACILITY OFFICIAL
(Chief Executive Officer or Legally Responsible Institutional Official)

SIGNATURE OF C.E.O. OR INSTITUTIONAL OFFICIAL r Print) (b)(6), (b)(7)c

DATE SIGNED 11/18/05

APHIS FORM 7023 (Replaces VS FORM 18-23 (OCT 88), which is obsolete.)
(AUG 91)

Q9 7

Animal Facility Locations
Center for Biologics Evaluation and Research/FDA
USDA Registration # 51-F-0024

(b)(2)High, (b)(7)f

Optional Column E Explanation Form

This form is intended as an aid to completing the Column E explanation. It is not an official form and its use is voluntary. Names, addresses, protocols, veterinary care programs, and the like, are not required as part of an explanation. A Column E explanation must be written so as to be understood by lay persons as well as scientists.

1. **Registration Number:** 51-F-0024

2. **Number of animals used in this study subject to column E listing:** 11

3. **Species (common name) of animals used in this study:** Guinea Pigs

4. **Explain the procedure producing pain and/or distress.**

   ASP# 89-32. This is a potency test that evaluates the presence of sufficient protective antigen in toxiods manufactured to prevent tetanus and diphtheria in humans. It is performed by CBER as a lot release test to verify adequate protection to the U.S. population by vaccines licensed in the U.S. Animals are injected with a combination of toxin and protective antibodies and survival is determined out to 7 days. Protected pigs show no sign, but control animals and inadequately protected animals will develop signs of disease and proceed to death rapidly without the benefit of euthanasia. Historically, 10 % of the total number of animals used have showed not signs of immunity and therefore have fallen under column E.

5. **Provide scientific justification why paid and/or distress could not be relieved. State methods or means used to determine that pain and/or distress relief would interfere with test results. (For Federally mandated testing, see question 6 below).**

   As required by the Minimum Standards (which are the precursors to the CFR) animals which become sick before 96 house cannot be euthanized. After 96 hours and up until the end of the test of 7 days, any animals showing signs of disease can be euthanized. There is no in vitro alternative for potency testing these two components of the U.S. Childhood Vaccination Program.

6. **What, if any, federal regulations require this procedure? Cite the agency, the Code of Federal Regulations (CFR) title number and the specific section number (e.g., APHIS, 9 CFR 113.102):**

   This test is required by the FDA Minimum Standards Requirements.

Optional Column E Explanation Form

This form is intended as an aid to completing the Column E explanation. It is not an official form and its use is voluntary. Names, addresses, protocols, veterinary care programs, and the like, are not required as part of an explanation. A Column E explanation must be written so as to be understood by lay persons as well as scientists.

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1. **Registration Number:** 51-F-0024

2. **Number of animals used in this study subject to column E listing:** 2

3. **Species (common name) of animals used in this study:** Guinea Pigs

4. **Explain the procedure producing pain and/or distress.**

Hemoglobin based oxygen carriers (HBOCs) are designed to provide optimal oxygen delivery to tissues in times of severe blood loss. Recently, certain HBOCs are being developed in part as adjunctive treatment of gram-negative sepsis. Several in vitro and murine models have suggested that lipopolysaccharide (LPS), which are in high concentration in gram-negative sepsis, accelerates HBOC oxidation leading to highly toxic forms of the heme protein and subsequent cellular/tissue injury and accelerated cell death and mortality. This study evaluates the potential problem of HBOC accelerated oxidation in the presence of LPS and subsequent morbidity and mortality in the guinea pig. Guinea pigs, like humans, cannot produce endogenous ascorbic acid. LPS depletes ascorbic acid in sepsis hence removing the primary plasma reducing agent, which prevents oxidation of HBOCs to toxic species. The pharmacokinetics of HBOC oxidative species, tissue injury (histopathology), plasma/tissue oxidative markers and mortality will be evaluated following LPS challenge (dose range: 0.05 – 10 mg/kg i.p.) and 20% HBOC exchange therapy. Animals in the high dose LPS arm of the study will likely expire within twenty-four hours. All animals will be euthanized after a twenty-four hour period.

5. **Provide scientific justification why paid and/or distress could not be relieved. State methods or means used to determine that pain and/or distress relief would interfere with test results. (For Federally mandated testing, see question 6 below).**

The scientific objective is to examine the possible toxicity of HBOC use during gram negative sepsis in humans. It is unavoidable that some animals will get very sick and possibly die from the LPS exposure. High dose animals are the most likely to get sick within the first 12 hours following exposure to LPS. Animals will be monitored hourly over the initial 12 hours and then at 18 and 24 hours. If animals exhibit pain and distress, as evidenced by abnormal movements (writhing) , paralysis, respiratory distress (labored breathing), or failure to respond to external stimuli, they will be euthanized immediately with an i.v. dose of pentobarbital (100 mg/mL). However, it is possible that a small percentage of animals may die or become severely moribund in between observations. These animals will be placed in column E.

6. **What, if any, federal regulations require this procedure? Cite the agency, the Code of Federal Regulations (CFR) title number and the specific section number (e.g., APHIS, 9 CFR 113.102):** N/A